REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

By the foregoing amendment, claims 1-18 and 20 have been amended. Support for the amendments to the claims can be found throughout the originally filed application. No new matter has been added.

Initially in the Official Action, the Examiner has indicated that only some of the certified copies of the priority documents have been received. It is noted that applicants will submit the certified copies of the foreign priority documents in due course.

Next the Examiner states that applicant has not complied with the conditions for receiving benefit of an earlier filing date under 35 U.S.C. § 120 since the first sentence of the specification has not been amended to provide the continuing data information. This is incorrect as applicants did specifically request that the first sentence of page 1 of the specification be amended to insert this appropriate information in the paragraph bridging pages 1 and 2 of the Utility Patent Application Transmittal Letter originally filed with the application on August 23, 2001.

Further, the Examiner has stated that the "IDS filed Augsut 23, 2001 has been received and is signed and considered . . . ." However, as may be seen from the Examiner-initialed copy attached to the Official Action, the Examiner has crossed out JP 62-89699 and JP 08-140677, and has not initialed the Cunningham et al. article. The Examiner has failed to indicate why these references which were timely submitted and in full compliance with the IDS procedures have not been considered.

The Examiner is respectfully requested to consider each of these references and provide applicants' with another Examiner-initialed copy of the PTO-1449 form indicating noting such consideration.

Turning now to the merits of the Official Action, the Examiner has rejected claims 2, 4, 6, 8, 15, 18 and 20 under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is respectfully traversed.

As to claims 2, 4, 6 and 8 applicants have amended the claims in order to expedite prosecution and not to acquiesce to the Examiner's rejection. Thus the Examiner's rejection in this regard is rendered moot.

Concerning claim 15, applicants have amended the claim in order to expedite prosecution and not to acquiesce to the Examiner's rejection. Support for this amendment can be found on at least page 25, line 21 to Page 26, line 4 of specification.

Lastly, as to claims 18 and 20, applicants have amended these claims, in order to expedite prosecution and not to acquiesce to the Examiner's rejection, so as to recite the methods of using the polypeptide. Support for such amendments can be found on at least page 45, lines 17-14 of specification.

In light of the above, the Examiner is respectfully requested to withdraw the rejection under 35 U.S.C. § 112, second paragraph.

Claims 1-17 have been rejected under 35 U.S.C. § 101 because the claimed invention is purportedly non-statutory subject matter. This rejection is respectfully traversed. However, to expedite prosecution and not to acquiesce to the Examiner's

rejection, independent claim 1 has been amended in accordance with the Examiner's suggestion to recite "isolated or purified" in the preamble. Accordingly, withdrawal of this rejection under 35 U.S.C. § 101 is respectfully requested.

The Examiner has rejected claims 1, 3, 5, 7 and 15-17 under 35 U.S.C. § 102(b) as allegedly being anticipated by Hashi et al. (U.S. Patent No. 5,302,701). This rejection is respectfully traversed.

For prior art to be anticipatory, every element of the claimed invention must be disclosed in a single item of prior art in the form literally defined in the claim. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986).

The first peptide included in the polypeptide set forth in currently pending claim 1 is defined by the amino acid sequence identified by SEQ ID NO. 1. The longest amino acid sequence (Ala^{2} to Trp^{341}) of SEQ ID NO. 1 recited in claim 1 for the first peptide is the amino acid sequence of the 260^{th}-599^{th} from the N-terminal of human Fibronectin (hereinafter "FN"), *i.e.*, Ala^{260}-Trp^{599} of FN. The amino acid within the range of Ala^{260} to Trp^{599} constitutes the collagen-binding domain of FN. Thus, the first peptide as recited in claim 1 includes at least parts of the collagen-binding domain of human FN.

The full functional region of FN consists of N-terminal - fibrin/heparin-binding domain (32K) - collagen-binding domain (40K) - cell-binding domain (140-150K) - (-S-S-) - C-terminal.

As apparent from above, the first peptide of claim 1 that forms the collagen-binding domain is thoroughly different from the peptide existent in the cell-binding domain of FN. Further, the amino acid sequence Ala^{260} to Trp^{599} of FN which is shown as the amino acid sequence Ala^{2} to Trp^{341} of the SEQ ID No. 1 is unique to

the collagen-binding domain of FN. No other domains of FN have such amino acid sequence Ala^{2} to Trp^{341} of SE ID NO. 1. No other nature protein having the same sequence of course is existent.

Moreover, the nature polypeptides have their unique conformations (protein structures), providing their own functions: the respective characteristics of FN, *i.e.*, fibrin/heparin-binding, collagen-binding, cell-binding (adhesive) activity are based on corresponding domain thereof each.

Further, not only are the collagen-binding domain and cell-binding domain of FN different domains, which respectively constitute FN, but also collagen-binding activity and cell-adhesive activity are different functional activities, distinctive from each other.

The first peptide of the above-mentioned sequence as described in the present application may be obtained by protease hydrolysis of FN. Being a proteolysis fragment of FN, this first peptide maintains the conformation (protein structure) included in collagen-binding domain of the natural FN. This is thus a mature peptide having the collagen-binding activity.

Also in view of this, the first peptide of currently claim 1 is significantly different from any other peptide which does not have collagen-binding activity, nor have the conformation for the specific function, but have an arbitrary sequence merely existent in FN.

The polypeptide of currently pending claim 1 comprising the first peptide mentioned above, and fused with a second peptide having another physiologically activity, is therefore a novel polypeptide.

Hashi et al. discloses a polypeptide construct comprising a polypeptide "X" having cell-adhesive activity like that of FN and a polypeptide "Z" having a cell growth promoting activity.

The polypeptide "X" of Hashi et al. is one of peptides which constitutes FN, but is quite different from the first peptide as recited in claim 1, since the first peptide has at least part of the amino acid sequence of Ala^{260} to Trp^{599} of FN while the polypeptide "X" of Hashi et al. has an amino acid sequence of Pro^{1239}-Met^{1517} of FN. Accordingly, the polypeptide construct of Hashi et al. is distinct from the polypeptide construct of claim 1.

Furthermore, the polypeptide construct of Hashi et al. has a function of fibronectin-like "cell adhesive activity". The "cell adhesive activity" should be distinguished from the "collagen-binding activity" in various functions of FN. In particular, "cell-adhesive activity" is effected in the presence of cell regardless of collagen, whereas "collagen-binding activity" is effected in the presence of collagen regardless of cell.

The functionality of the polypeptide "X" of Hashi et al. is "cell adhesive activity", and not "collagen-binding activity".

Hashi et al. reported that FGF-activity of "Z" has maintained in the polypeptide construct after fusing with the polypeptide "X", although, the FGF-activity of the polypeptide construct is in comparing to the control polypeptide "X" (not FGF) which is from FN and FGF-inactive. In addition, Hashi et al. showed the FGF-activity in a extremely high concentration such as 100nM and 1μM of FGF (see, example 2(A) and (B), respectively). This concentration is an abnormal one that is 10^2-10^3 fold as an ordinary one in such tests for FGF physiological activity. FGF should not be used

in such high concentration for assaying physiological activity when the FGF-activity could be maintained in the polypeptide construct in using of FGF-peptide with an ordinary concentration.

In other words, it is suggested that the polypeptide construct of Hashi et al. which is obtained by using the peptide from cell-binding domain of FN as a fusion partner is difficult to exhibit FGF-activity of FGF-peptide.

Hashi et al. also fails to disclose the use of a peptide from the collagen-binding domain of FN for polypeptide construct and a resulting polypeptide construct therefrom which maintains the collagen-binding activity and another physiologically activity from the fusion partner. As such it fails to teach each and every element of applicants' claimed invention and thus cannot be anticipatory prior art. Hence, the Examiner is respectfully requested to withdraw this rejection.

The Examiner has also made the following rejections under 35 U.S.C. § 103(a):

(1) claims 9-13 have been rejected as supposedly being unpatentable over Hashi et al. in view of Tuan et al.;

(2) claims 1-8 and 18 have been rejected as supposedly being unpatentable over Hashi et al. in view of Irani et al.;; and

(3) claims 19-20 has been rejected as supposedly being unpatentable over Hashi et al. in view of Geistlich et al.

Each of these rejections under 35 U.S.C. § 103(a) are respectfully traversed.

As discussed above, Hashi et al. fails to disclose the claimed invention. Hashi et al. also fails to suggest the claimed invention either alone or in combination with

the references cited by the Examiner above. None of Tuan et al. Irani et al. nor Geistlich et al. remedy the serious deficiencies of the Hashi et al. reference.

In particular, Tuan et al. discloses a polypeptide construct comprising the collagen-binding decapeptide from von Willebrand factor and a TGF-β. However, Tuan et al. demonstrated the hybrid polypeptide recovered from inclusion body in *E.coli* exhibited impaired collagen-binding activity as well as reduced physiological activity. It is also demonstrated that the decapeptide of Tuan et al. is inappropriate for the genetically engineered production of collagen-binding physiologically active polypeptide (see, page 5, line 9 to page 6, line 19 of the specification of the present application).

Thus, even if availability of protein such as cytokines of a genetically engineered production is needed as the Examiner pointed out, both Hashi et al. and Tuan et al. are not only completely silent about the use of a peptide from the collagen-binding domain of FN, but also could never teach obtaining the polypeptide construct which exhibits both collagen-binding activity and physiologically activity of a cytokine when using the peptide originating from said collagen-binding domain of FN.

Accordingly, Hashi et al. in view of Tuan et al. fails to render the claimed invention obvious.

On page 8 of the Official Action, the Examiner has stated that "Hashi et al. and Nishi et al. demonstrate that one of ordinary skill in the art would have made and used the claimed invention prior to the time the claimed invention was made." See also page 10 of the Official Action. However, Nishi et al. was never indicated as being included in any of the rejections. Thus, these citations to Nishi et al appear to

be in error. Nonetheless, Nishi et al., whether combined with Hashi et al. are taken alone, fails to teach or suggest the claimed invention.

Nishi et al. discloses hybrid polypeptides of bFGF or EGF with the collagen-binding polypeptide from collagenase of *Clostridium histolyticum*, which is an anaerobic Gram-negative bacillus, and which is different from the collagen-binding peptide from FN. Nishi et al. reported that the collagen-binding activity of the collagen-binding growth factors produced in their attempt was insufficient and their product failed to bind to the culture dishes coated with collagen as well as to many types of collagen materials (Proc. Natl. Acad. Sci. USA, vol. 95, pages 7018 to 7023 (1998)). Of course, such collagen-binding growth factors can not exhibit cell-growth promoting activity after its binding to collagen, since they cannot bind to the collagen materials. The collagen-binding growth factors were also found to experience decrease in their EGF activity.

Accordingly, even if Nishi et al., who has no disclosure of the collagen-binding peptide from FN, is combined with Hashi et al., such combination would not teach or suggest constructing the polypeptide utilizing the peptide from the collagen-binding domain of FN or obtaining the polypeptide which exhibits both collagen-binding activity and physiologically activity of a cytokine when using the peptide originating from said collagen-binding domain of FN.

Irani et al. discloses a hybrid protein comprising a cross-linking domain (1), two domains that promote inter-chain cross-linking (2 and 4) and a tissue-binding domain (3), and also the amino acid sequence Gly^{282}-Ser^{608} of FN as a tissue-binding domain (3). The amino acid sequence Gly^{282}-Ser^{608} of FN recited in Irani et al. corresponds to the amino acid sequence Gly^{251}-Ser^{577} of human FN, and is

different from the amino acid sequence Ala^{260} -Trp^{599} of the first peptide according to claim 1. Further, the hybrid protein of Irani et al. should have cross-linking and tissue-binding activities, but not have collagen-binding activity.

Irani et al., not only fails to disclose any concrete example of the hybrid protein including the above domain, but also fails to disclose or suggest anything about a fusion protein having both collagen-binding activity and another physiological activity. Therefore, even if one of ordinary skill in the art would have been motivatated to combine Irani et al. with Nashi et al., the combination of references still fail to teach or suggest the claimed invention.

Finally, Geistlich et al., either alone or in combination with Hashi et al., does not disclose or suggest that the polypeptide construct with collagen-binding activity and another physiological activity is effected by using the specific peptide having the amino acid sequence selected from the group consisting Ala^{260} to Trp^{599} and any other domains of human FN defined within SEQ ID No.1 in claim 1 of the present invention as a peptide partner of a physiological peptide.

In view of the above, the claimed invention is not obvious over the combination of references as set forth above. Thus, all of the Examiner's rejections under 35 U.S.C. § 103(a) should be withdrawn.

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this Amendment and Reply, or the application in general, it would be appreciated if the Examiner would

telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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